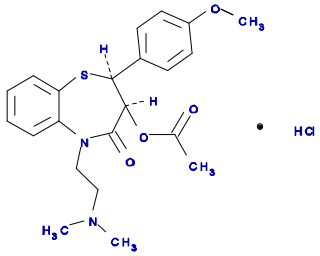
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES

(TWICE A DAY DOSAGE)

DESCRIPTION

Diltiazem hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). The chemical name for diltiazem is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2, 3-dihydro-2-(4-methoxyphenyl)-monohydrochloride,(+)-cis-. The structural formula is:



$C_{22}H_{26}N_2O_4S \cdot HCl$

Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.99. Each diltiazem extended-release capsule, for oral administration, contains either 60 mg, 90 mg, or 120 mg diltiazem hydrochloride. In addition, each capsule contains the following inactive ingredients:.....

[*NOTE: We note that in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance). We believe this is an important public health measure. Please respond accordingly by correctly noting the inactive ingredients present in this product.*]

CLINICAL PHARMACOLOGY

The therapeutic effects of diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action

Diltiazem hydrochloride produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect,

whereas there is only a modest fall in blood pressure in normotensives.

Hemodynamic and Electrophysologic Effects

Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Increased heart failure has, however, been reported in occasional patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem.

Diltiazem hydrochloride extended-release produces antihypertensive effects both in the supine and standing positions. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects. Diltiazem hydrochloride extended-release decreases vascular resistance, increases cardiac output (by increasing stroke volume), and produces a slight decrease or no change in heart rate. During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually reduced. Heart rate at maximum exercise does not change or is slightly reduced. Chronic therapy with diltiazem produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem hydrochloride extended-release antagonizes the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio.

Intravenous diltiazem hydrochloride in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory

periods by approximately 20%. In a study involving single oral doses of 300 mg of diltiazem in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length(up to 50% in some cases).

Chronic oral administration of diltiazem hydrochloride in doses of up to 360 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation. (See WARNINGS).

Pharmacokinetics and Metabolism

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%. Diltiazem undergoes extensive metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show diltiazem is 70% to 80% bound to plasma proteins. Competitive in vitro ligand binding studies have also shown diltiazem binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Minimum therapeutic plasma levels of diltiazem appear to be in the range of 50-200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single study in patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

Diltiazem is absorbed from the extended-release capsule formulation to about 92% of a reference solution at steady-state. A single 120 mg dose of the capsule results in detectable plasma levels within two to three hours and peak plasma levels at six to 11 hours. The apparent elimination half-life after single or multiple dosing is five to seven hours. A departure from linearity similar to that observed with the diltiazem hydrochloride tablet is observed. As the dose of

diltiazem hydrochloride extended-release capsules is increased from a daily dose of 120 mg (60 mg bid) to 240 mg (120 mg bid) daily, there is an increase in area-under-the-curve of 2.6 times. When the dose is increased from 240 mg to 360 mg daily, there is an increase in area-under-the-curve of 1.8 times. The average plasma levels of the capsule dosed twice daily at steady-state are equivalent to the tablet dosed four times daily when the same total daily dose is administered.

INDICATIONS AND USAGE

Diltiazem hydrochloride extended-release capsules are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive medications, such as diuretics.

CONTRAINDICATIONS

Diltiazem is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second-or-third AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1.Cardiac Conduction Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patient with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second-or-third-degree AV block (nine of 2,111 patients or 0.43%). Concomitant use of diltiazem with beta blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2.Congestive Heart Failure Although diltiazem has a negative inotropic effects in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a

reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ±6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of diltiazem hydrochloride in combination with beta blockers in patients with impaired ventricular functions is limited. Caution should be exercised when using this combination.

3.Hypotension Decreases in blood pressure associated with diltiazem therapy may occasionally result in symptomatic hypotension.

4.Acute Hepatic Injury Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some. (See PRECAUTIONS).

PRECAUTIONS

General

Diltiazem hydrochloride is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a

dermatologic reaction persist, the drug should be discontinued.

Drug Interactions

Due to the potential for additive effects, caution and careful titration are warranted in patients receiving diltiazem concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with diltiazem. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. Diltiazem undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of diltiazem with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.

Beta-Blockers. Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS).

Cimetidine. A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1 week course of cimetidine at 1,200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, non-significant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem

may be warranted.

Digitalis. Administration of diltiazem with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem therapy to avoid possible over-or under-digitalization. (See WARNINGS.)

Anesthetics. The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Cyclosporine. A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted or discontinued. The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Carbamazepine. Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40 to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 24 month study in rats and a 21 month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response *in vitro* bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy: Teratogenic Effect -Pregnancy Category C

Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have

been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use diltiazem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Serous adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either diltiazem tablets or diltiazem hydrochloride extended-release capsules as well as experience observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse

events were edema (9%), headache(8%),dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing(3%), and first degree AV block(3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving diltiazem tablets or diltiazem hydrochloride extended-release capsules were (ie, greater than 1%) edema (5.4%), headache(4.5%), dizziness(3.4%), asthenia(2.8%), first degree AV block (1.8%), flushing(1.7%), nausea(1.6%), bradycardia(1.5%), and rash(1.5%).

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS		
Adverse	Diltiazem N=315 # pts(%)	Placebo N=211 # pts(%)
headache	38(12%)	17(8%)
AV block first degree	24(7.6%)	4(1.9%)
dizziness	22(7%)	6(2.8%)
edema	19(6%)	2(0.9%)
bradycardia	19(6%)	3(1.4%)
ECG abnormality	13(4.1%)	3(1.4%)
asthenia	10(3.2%)	1(0.5%)
constipation	5(1.6%)	2(0.9%)
dyspepsia	4(1.3%)	1(0.5%)
nausea	4(1.3%)	2(0.9%)
palpitations	4(1.3%)	2(0.9%)
polyuria	4(1.3%)	2(0.9%)
somnolence	4(1.3%)	_
alk phos increase	3(1%)	1(0.5%)

hypotension	3(1%)	1(0.5%)
insomnia	3(1%)	1(0.5%)
rash	3(1%)	1(0.5%)
AV block second degree	2(0.6%)	_

In addition, the following events were reported infrequently (less than 1%) with diltiazem hydrochloride extended-release capsules or diltiazem hydrochloride tablets or have been observed in angina or hypertension trials.

Cardiovascular: Angina, arrhythmia, second-or-third-degree AV block (see conduction warning), bundle branch block, congestive heart failure, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tremor.

Gastrointestinal: Anorexia, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, and LDH (see Hepatic Warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, sexual difficulties, tinnitus.

The following postmarketing events have been reported infrequently in patients receiving diltiazem: alopecia, erythema multiforme, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. There have been observed cases of a generalized rash, characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between these events and diltiazem therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge)has also been reported.

OVERDOSAGE OR EXAGGERATED RESPONSE

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg.

The toxic dose in man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases.

There have been 29 reports of diltiazem overdose in doses ranging from less than 1 g to 10.8 g. Sixteen of these reports involved multiple drug ingestions.

Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 g to 10.8 g. There were seven reports with a fatal outcome; although the amount of diltiazem ingested was unknown, multiple drug ingestions were confirmed in six of the seven reports.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favorably to atropine, as did heart block, although cardiac pacing was also frequently utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure and in cases of cardiac failure inotropic agents were administered. In addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, and/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose was conflicting.

In the event of overdose or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences the following measures may be considered:

Bradycardia: Administer atropine (0.6 to 1 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

High-Degree AV Block:	Treat as for bradycardia above. Fixed high-degree block should be treated with cardiac pacing.
Cardiac Failure:	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension:	Vasopressors (eg, dopamine or norepinephrine bitartrate)

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION:

Dosages must be adjusted to each patient's needs, starting with 60 to 120 mg twice daily. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy; therefore, dosage adjustments should be scheduled accordingly. Although individual patients may respond to lower doses, the usual optimum dosage range in clinical trials was 240 to 360 mg/day.

Diltiazem extended-release capsules has an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of diltiazem hydrochloride extended-release or the concomitant antihypertensives may need to be adjusted when adding one to the other. See WARNINGS and PRECAUTIONS regarding use with beta-blockers.

HOW SUPPLIED

- Strength and established name of the dosage form.

- Packaging and NDC numbers.

- Color, imprinting or other identifying characteristics.

- Storage and dispensing information.

- Caution: Federal law prohibits dispensing without prescription.

- Manufactured by and/or distributed by statement and date of the latest revision.